REMARKS

Claims 1, 4, 7 and 8 are now pending in the application. Claims 2, 3, 5 and 6 have been cancelled herewith to comply with the Examiner's request to cancel claims reciting the non-elected groups. Applicants reserve the right to file divisional/continuation applications directed to the subject matter of Claims 2 and 5 in future prosecution. Claims 7 and 8 are new. Support for the new claims can be found throughout the specification, for example, at page 35, lines 6-25 and page 36, lines 1-21. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

Claims 1, 3, 4, 6 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention. With respect to the rejection of Claims 3 and 6, these claims have been cancelled herewith and thus the rejection of these claims is rendered moot. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the presently amended Claims 1 and 4 and claims dependent thereon are fully enabled under 35 U.S.C. § 112, second paragraph.

A. Claim 1 is rejected for indefiniteness allegedly due to a lack of clarity of the claim language for failing to recite a final process step, which agrees back with the preamble. (Action at page 3). Specifically, the Action states that the interaction analysis step fails to indicate a relationship to the stated objective of displaying characteristics of a compound.

Applicants have amended Claim 1 to recite a final process step of assigning an activity prediction value to each atom of said plurality of molecules and displaying said activity prediction value on a graphical display. Support for the present amendment can be found in Figure 1, and page 30, lines 20-23 of the originally filed specification.

B. Claim 1 is presently rejected for indefiniteness due to having a preamble which is directed to structure-activity by a claim body that allegedly fails to recite a step directed to determining any activity. (Action at page 3).

Applicants have amended Claim 1 to calculate an activity prediction formula which is subsequently used to provide an activity prediction value to each atom of said plurality of molecules. Support for the present amendments can be found in Figure 1, page 30, lines 20-25 and page 31, lines 1-18 of the originally filed specification.

C. Claim 1 is presently rejected for indefiniteness for allegedly not making clear what "characteristics" are meant to be "extracted and visually displayed". (Action at page 3).

Applicants have amended the preamble to clarify that the characteristics are physiochemical characteristics of the compound. Support for the present amendment can be found throughout the specification, for example, at page 48, lines 3-8 of the originally filed specification.

D. Claim 1 is presently rejected for indefiniteness due to recitation of the term "superposing" which is alleged to be unclear. (Action at page 4).

Applicants have amended step A to recite: "superposing a three-dimensional spatial arrangement of a plurality of molecules using Cartesian three-dimensional x, y, and z atomic coordinates in a virtual space". As such the Applicants have clarified that what is superposed are molecules using their three-dimensional x, y, and z atomic coordinates. Applicants respectfully submit that the superposition of such atomic coordinates of various molecules is not unclear to one of ordinary skill in the art. Support for such an amendment can be found throughout the specification, for example, on page 26, lines 18-23 and Figure 2(A).

E. Claim 1, step C and step B1 is presently rejected for indefiniteness due to reciting the term "respective" in the phrase "respective atoms" which is alleged to be unclear. (Action at page 4).

Applicants have deleted the term "respective" and in each instance, refer to the atoms of the plurality of molecules superposed. Applicants respectfully submit that the instant amendment clarifies which atoms are being superposed

and which atoms are being used to calculate interaction with the represented points recited in step C.

F. Claim 1, step C is presently rejected for indefiniteness because the meaning of calculating interactions between atoms and points is allegedly not clear. (Action at page 4).

Applicants have amended step C to recite: "a process C of calculating interactions selected from the group consisting of steric interactions, electrostatic interactions, hydrophobic interactions and combinations thereof between the atoms of said plural molecules thus superposed and said represented points using an evaluation function..." Therefore, the amended claim recites that the atoms of the molecule being determined is analyzed by calculating the steric interactions, and/or electrostatic interactions and/or hydrophobic interactions using one or more evaluation functions such as those described on page 30, lines 1-4. Several examples of evaluation functions and their specific selection for each of the interactions are presented in the originally filed application at pages 30, lines 1-19, and pages 34-67.

G. Claim 1, step D is presently rejected for indefiniteness because the nature of "calculating interactions" and how the interactions are being analyzed are allegedly not clear. (Action at page 5).

Applicants have amended step D in Claim 1 and 4 to recite: "a process D of statistically analyzing said interactions using statistical analysis to generate a

plurality of correlation components between said calculated interactions and a known pharmacological activity of one of said molecules and forming an activity prediction formula..." As such, the interactions (one or more of steric, electrostatic and hydrophobic) are calculated per step C. The resulting interaction results are analyzed using a partial least square method as disclosed on page 30, lines 20-21, and page 31, lines 1-18 and page 38, lines 22-25 and page 39, lines 1-18 of the originally filed application.

Accordingly, Applicants respectfully request that the present rejection of Claims 1 and 4 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 101/ 112-1

Claims 1, 3, 4, 6 stand rejected under 35 U.S.C. § 101 because the claimed invention allegedly lacks patentable utility because the claims are not supported by either specific and/or substantial utility or a well established utility. With respect to the rejection of Claims 3 and 6, these claims have been cancelled herewith and thus the rejection of these claims is rendered moot. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the claims as amended provide specific, substantial and well established utility.

Claims 1, 3, 4, 6 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific and substantial

asserted utility or a well established utility. This rejection is respectfully traversed.

Amended Claim 1 recites:

> A three-dimensional quantitative structure-activity relationship method for determining and visually displaying physiochemical characteristics of a compound which modulates a pharmacological activity of said compound...
>
> a process E of assigning an activity prediction value to each atom of said plurality of molecules and displaying said activity prediction value on a graphical display,...

Applicants respectfully submit that the amended Claims 1 and 4 recite a method for determining and visually displaying the physiochemical properties of a compound, which can also be an unknown compound and a program for a three-dimensional quantitative structure-activity relationship method for determining and visually displaying physicochemical characteristics of a compound respectively. The methods provide for computation and modeling of complex structure-function characteristics with fewer computer resources more rapidly, display in 3D, complex molecular interactions and provide real-world information about the molecule's structure-function relationship. The amended claims provide steps for the calculation of an atomic coordinate model by providing one or more represented points as shown in Figure 3. Each of the represented points is used to calculate one or more of steric, electrostatic and hydrophobic interactions between the represented points and the atoms of the molecule. The interactions can then be used to determine which atomic regions impact activity

of the molecule (or unknown compound) by performing one or more partial least squares analyses using data sets related to activity (for example CoFMA data) to derive a structure-activity relationship formula (See Figure 3 and page 30, lines 20-25 and page 31, lines 1-18). The structure-activity relationship formula can then be used to assign a visual marker which reflects the atomic regions where activity can be enhanced or weakened using a specific interaction.

Specific examples of utility can include the elimination of large data sets representing lattice points in order to obtain an accurate molecular 3D quantitative structure-activity relationship. (See specification at page 8, lines 22-25, page 9, lines 1-9 and page 18, lines 4-12). Other examples specific and/or substantial utility embodied in the amended claims can be found on page 11, lines 2-14, which include broader computation of structure-function activity using a wider array of computer resources, elimination of singularity and cut-off associated with other modeling processes and overcoming the difficulty associated with modeling the structure-activity of difficult atom types.

Accordingly, Applicants respectfully request that the present rejection of Claims 1 and 4 under 35 U.S.C. § 101 be reconsidered and withdrawn.

Claims 1, 3, 4, 6 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is allegedly not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. With respect to the rejection of Claims 3 and 6, these claims have been cancelled herewith and thus the

rejection of these claims is rendered moot. This rejection is respectfully traversed.

Applicants respectfully submit, that the presently amended claims provide specific, substantial and well established utility as explained above. In addition, one of ordinary skill in the art could use the present inventions embodied in the claims as amended to identify and synthesize new compounds which have enhanced or favorable activity based on 3D-structure-activity calculations of compounds of known activity. Parameters including steric interactions, electrostatic interactions and hydrophobic interactions can be calculated, evaluated and graphically assigned to atoms in unknown compounds which provide valuable information in the synthesis of novel compounds with fewer computing resources as required by "Comparative Molecular Field Analysis" (CoMFA) and "Comparative Molecular Similarity Analysis" (CoMSIA) methods of 3D quantitative structure-activity relationship analysis. Tangible results from the claimed methods can be readily observed in Figures 48-50 which illustrate how one of ordinary skill in the art can use the methods of the present invention to determine the contribution of electrostatic, steric and hydrophobic interactions on the activity of cyclooxygenase (COX-2) inhibitors. Displaying the aforementioned interactions in 3D permits rapid and simplified molecular modeling of compounds with enhanced activity and enables one of ordinary skill in the art to steer away from the synthesis of molecules with unfavorable activity. (See specification at pages 65-67). Therefore, the Applicants have provided concrete examples of

how one of ordinary skill in the art can make and use the methods of the present invention to derive credible and well established utility.

Accordingly, Applicants respectfully request that the present rejection of Claims 1 and 4 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 101 (NON-STATUTORY INVENTION)

Claims 1, 3, 4, 6 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. With respect to the rejection of Claims 3 and 6, these claims have been cancelled herewith and thus the rejection of these claims is rendered moot. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the amended claims produce a useful, tangible and concrete result relating to quantitative structure-activity relationships in a molecule or unknown compound.

(i) The Claims As Amended Provides A Useful Result

Applicants have demonstrated above, that Claims 1 and 4 are directed to methods for determining and visually displaying physiochemical characteristics of a compound which modulates a pharmacological activity of said compound. Such a method overcomes several disadvantages described in the present application and provides useful results in terms of reduced computing resources required to perform such complex 3D quantitative structure-activity relationship calculations. Moreover, the present methods have been validated to provide

detailed information concerning steric interactions, electrostatic interactions and hydrophobic interactions atoms in a compound that permits one of ordinary skill in the art to synthesize molecules that have enhanced activity as compared to a first generation pharmacological molecule.

(ii) The Claims As Amended Provided Provide Tangible Results

Applicants respectfully submit, that the amended Claims 1 and 4 and claims dependent thereon provide tangible results as defined in the Action at page 10. Essentially, this prong of the utility requirement of U.S.C. § 101 requires that the methods embodied by the claims provide a "real-world result". (Action at page 10).

Applicants have shown above how the amended Claims 1 and 4 provide real-world results from the practice of the methods. For example:

- The number of points required to provide statistically reliable activity prediction effects due to physiochemical interactions are significantly reduced in the embodiments of the present invention as compared to CoFMA, CoMSIA and MFA approaches to 3D structure-activity relationship modeling methods. The reduction of points required to produce such visual 3D structure-activity relationship modeling translates to the real-world result of being able to perform the modeling using remarkably less computing and memory resources, such that the modeling can be

performed using standard PCs rather than specialized computers; and

- Atomic coordinates calculated using the present methods utilize xyz coordinates obtained by weighted averaging of xyz coordinates of atoms and pseudo-atoms which are equal to or smaller than a predetermined threshold value. The real-world result obtained is that the same structure-actvity relationship between atoms is obtained no matter how the molecules are oriented relative to the xyz axes.

(iii) The Claims As Amended Provide Concrete Results

The Action alleges that the methods in the instant application are not concrete, because it does not seem to be producing the same result if repeated by another person. In support of this allegation, the Action asserts that "[T]he method comprises a step of 'subjective superposition of different molecules one atop the other by a researcher' which will result in a method that is not 'concrete'". (Action at page 11).

Applicants respectfully submit that the Applicants have provided a method of molecular superposition which is faster and non-arbitrary. (See specification at page 3, lines 6-15). The non-arbitrary nature of the superposition is solved by using an evaluation function for example a Gaussian evaluation formula or indicator coefficients. The Action cites the specification at page 2:

> "the approach of superposing atoms with each other or functional groups with each other has a disadvantage that researcher's subject is inevitably

> reflected. For instance, subjective superposition of different molecules one atop the other by a researcher may result in something which is quite different from superposition of conformations in which actual molecules interact with receptor proteins."

(Specification at page 2, lines 17-23).

Applicants respectfully assert that the problems associated with subjective placement described in the above passage relates to methods that do not employ an evaluation function. The specification discloses on page 3, lines 3-13:

> "Although an approach using an evaluation function is ideal as a molecular superposition procedure per se, this approach has a flaw that computation takes time. Noting this, the inventors of the present invention have discussed development of a molecular superposition method which is faster and non-arbitrary, and invented and reported a method which a standard PC can execute at a computation speed which is 100 through 1000 times as fast as that of conventional methods (Kotani, T.; Higashiura, I. Rapid evaluation of molecular shape similarity index using pairwise calculation of the nearest atomic distances. J. Chem. Inf. Comput. Sci. 2002, 42, 58-63.)."

The Applicants respectfully submit that the arbitrariness alluded to by the Action is ameliorated in the present embodiments because the cluster analysis and evaluation functions employed in the present methods serve to remove such researcher's subjective effects.

Applicants respectfully submit that Claims 1, 4 and claims dependent thereon are statutory i.e. they are directed to methods or processes in that they transform xyz coordinates of a plurality of atoms superposed in virtual space data into activity prediction data that can be used to model unknown compounds having

enhanced activity when compared to molecules of known structure and activity. The methods disclosed in the present invention produce a useful, tangible and concrete result as required by 35 U.S.C. § 101.

Accordingly, Applicants respectfully request that the present rejection of Claims 1 and 4 under 35 U.S.C. § 101 be reconsidered and withdrawn.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: July 11, 2008

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